REMARKS

Claims 3, 9-17, 25, 26 and 28-38 were pending in the application. According to the foregoing amendments, claims 3, 34 and 37 have been amended and new claims 39 and 40 have been added. Accordingly, after the amendments presented herein have been entered, claims 3, 9-17, 25, 26 and 28-40 will remain pending in this application.

Support for the amendments to the claims may be found throughout the specification and in the claims as originally filed. Specifically, support for the amendment to claims 3 and 37 can be found throughout the specification, for example, at page 1 of Table 1; at page 23, line 35 to page 24, line 12; and at page 24, line 35 to page 25, line 20, and in the claims as originally filed.

Claims 25, 26 and 28-35 were previously withdrawn in response to the Restriction Requirement set forth in the Office Action of January 17, 2006. Applicants respectfully submit that claims 25, 26 and 28-35 are method claims capable of re-joinder in accordance with the provisions of MPEP § 821.04.

No new matter has been added by the claim amendments or the introduction of the new claim. The amendments to the claims should not be construed as an acquiescence to the validity of the Examiner's rejections and were done solely in the interest of expediting prosecution and allowance of the claims. Applicants reserve the right to pursue the claims as originally filed in one or more further applications.

The Term "Complement"

At paragraph 1 of the present Office Action, Examiner states that "[t]he term 'complement' in claim 3 is interpreted to mean the full and complete complement of a sequence."

Applicants confirm that for purposes of the present application only, the term "complement" will denote the full complement of a sequence.

Election/ Restrictions

Applicants acknowledge the election of Group I, *i.e.*, claims 1-17 and 36-38, in response to the restriction requirement under 35 U.S.C. § 121 as set forth in the Office Action of January 17, 2006. With regard to the remaining method claims, it is Applicants' understanding that once a composition claim is found to be allowable, the pending method claims that depend from or

otherwise include all the limitations of an allowable composition claim will be re-joined in accordance with the provisions of MPEP § 821.04. Accordingly, Applicants respectfully request re-joinder of such claims (*e.g.*, claims 25, 26 and 28-35) when the pending composition claims are found to be allowable.

Rejection of Claims 3, 9-17 and 36-38 Under 35 U.S.C. § 101

The Examiner has rejected claims 3, 9-17 and 36-38 under 35 U.S.C. § 101 because allegedly "the claimed invention lacks patentable utility." In particular, the Examiner is of the opinion that

> [t]he claimed polynucleotide is not supported by a specific and substantial asserted utility because the disclosed uses of the polynucleotides are not specific and substantial. The specification states that the nucleic acid compounds may be useful as probes for identification of Corynebacterium glutamicum, however this utility is not specific to the claimed polynucleotide. The specification states that the claimed polynucleotide may be used as a diagnostic for the pathogen Corynebacterium diptheriae, however the assertion is not credible because no evidence is presented that Corynebacterium diptheriae comprises polynucleotide sequences that would hybridize under conditions sufficiently stringent that would allow the claimed polynucleotide to be used in a diagnostic assay. The specification states that the claimed polynucleotide could be used for conducting research to characterize the role and effect of the gene product. The research contemplated by the applicants to characterize potential protein products, especially their biological activities, does not constitute specific and substantial utility. Identifying and studying the properties of a protein itself or the mechanisms in which the protein is involved does not define a "real world" context or use. The specification states in Table 1 that SEQ ID NO: 5 encodes a CysQ ammonium transport protein, however the specification does not contain any evidence that the assertion is correct. The specification does not show in Table 4, page 1 that the sequence RXA00104 (which corresponds to SEQ ID NO:5, as stated in Table 1) has any level of homology to a CysQ gene.
>
> Neither the specification as filed nor any art of record discloses or suggests any property or activity for the claimed polynucleotide such that another non-asserted utility would be well established.

Applicants respectfully traverse the foregoing rejection for the following reasons. Initially, Applicants submit that, as set forth in MPEP § 2164.07, "[t]he examiner has the initial burden of challenging an asserted utility. Only after the examiner has provided evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince one of ordinary skill in the art of the invention's asserted utility (citations omitted)." Applicants respectfully

submit that the Examiner has not overcome this burden. Indeed, the Examiner has presented no evidence to indicate that Applicants' assertions are incorrect. While the Examiner asserts that Applicants have failed to provide any evidence, the burden, in fact, is on the Examiner to demonstrate that Applicants' assertions are incorrect.

Contrary to the Examiner's assertions, Applicants respectfully submit that a *well established utility* is immediately apparent from Applicants' specification and the knowledge in the art at the time of Applicants' invention. Specifically, Applicants have disclosed in the instant specification that SEQ ID NO:5 encodes a cysQ molecule that shows homology to other cysQ molecules known in the art.

In this regard, Applicants direct the Examiner's attention to Example 10 of the *Revised Interim Utility Guidelines* (hereinafter referred to as the "Guidelines"). Specifically, Example 10 of the Guidelines sets forth that a claim directed to "[a]n isolated and purified nucleic acid comprising SEQ ID NO:2" possesses a well established utility where the specification and the art discloses the following

> [t]he specification discloses a Table that indicates that one member of the library having SEQ ID NO:2 has a high level of homology to a DNA ligase. The specification teaches that this complete ORF (SEQ ID NO:2) encodes SEQ ID NO:3. An alignment of SEQ ID NO: 3 with known amino acid sequences of DNA ligases indicates that there is a high level of sequence conservation between the various known ligases. The overall level of sequence similarity between SEQ ID NO:3 and the consensus sequence of the known DNA ligases that are presented in the specification reveals a similarity score of 95%. A search of the prior art confirms that SEQ ID NO: 2 has high homology to DNA Ligase encoding nucleic acids and that the next highest level of homology is alpha-actin. However the latter homology is only 50%. Based on the sequence homologies, the specification asserts that SEQ ID NO: 2 encodes a DNA ligase.
>
> Based on the foregoing fact pattern, the Guidelines provide that
>
> [b]ased on the record, is there a 'well established utility' for the claimed invention? Based upon applicant's disclosure and the results of the PTO search, there is no reason to doubt the assertion that SEQ ID NO: 2 encodes a DNA ligase. Further, DNA ligases have a well-established use in the molecular biology art based on this class of protein's ability to ligate DNA. Consequently the answer is yes.

Accordingly, the Guidelines provide that where an invention is directed to an open reading frame characterized, based on a homology analysis, as a protein of known function and use, that invention possesses a well established utility. Consistent with this standard, the present

specification teaches that based, in large part, on sequence homology analysis, SEQ ID NO: 5 encodes a cysQ protein (see page 1 of Table 1 of the specification).

Moreover, the specification provides evidence to support Applicants' functional characterization of the claimed sequences. Indeed, as taught in the specification, the functional characterization of the claimed sequences was performed by reliable and well established methods, based, in large part, on sequence homology analysis to known sequences. Applicants direct the Examiner's attention to Example 3 of the specification where Applicants teach that the sequences of the invention were characterized by computational functional analysis (see page 50, lines 1-8). In Example 11 at page 57, line 9 to page 58, line 28 of the specification, Applicants clarify that sequence homology analysis was used to characterize the claimed sequences. Specifically, functional analysis of the claimed sequences was performed by use of the WIT System, from Integrated Genomics (Chicago, IL). The assignment of function by the WIT software involved the integration and analysis of numerous factors, including, in large part, the comparative analysis of genomes, to generate cellular reconstructions of pathways (see Overbeek *et al.* "WIT: integrated system for high-throughput genome sequence analysis and metabolic reconstruction" (2000) *Nucleic Acids Research* 28(1):123-125, a copy of which is attached herein as Appendix A). Sequence homology analysis represented a significant aspect of functional characterization by the WIT system. Specifically, the FASTA program was used to search sequence databases and evaluate similarity scores (see Pearson *et al.* "Improved tools for biological sequence comparison" *Proc. Natl. Acad. Sci. USA* (1988) 85:2444-2448, a copy of which is attached herein as Appendix B). Based on the foregoing analysis, SEQ ID NOs: 5 and 6 were functionally characterized by Applicants as encoding a cysQ protein.

The analysis and functional characterization of proteins using these techniques were well accepted by the scientific community at the time of the filing of the present application. Indeed, as described in Koonin *et al.* ("Beyond complete genomes: from sequence to structure and function" *Current Opinion in Structural Biology* (1998) 8:355-363), a copy of which is attached herein as Appendix C, using a variety of factors, including, for example, analysis of paralog clusters, structural comparisons with homologous proteins, analysis of evolutionarily conserved pathways, and sequence comparisons, a reliable identification of protein function can be achieved, particularly in light of the elucidation of protein superfamilies. Accordingly, one skilled in the art would find the results of such functional analysis reliable and would reasonably

conclude that Applicants' assertions in the specification that the claimed nucleotide and amino acid sequences (SEQ ID NOs:5 and 6, respectively) have a cysQ function are accurate.

Moreover, Applicants submit that ***post-filing date experimental evidence, based on sequence homology, confirms Applicants' functional characterization of SEQ ID NOs:5 and 6***, as taught by the specification. Specifically, Applicants direct the Examiner's attention to GenBank entries having Accession Nos. CAF19551, BAB98238 and YP_225137 (each of which published after Applicants' filing date and copies of which are attached herein as Appendices D, E and F, respectively). SEQ ID NO:6 of the present invention shares a 100% identity over the entire amino acid sequences set forth in each of GenBank Accession Nos. CAF19551, BAB98238 and YP_225137 (see alignments set forth as Appendices G, H and I). Moreover, each of these ***GenBank entries confirm Applicants' identification of the claimed molecule as a cysQ gene from Corynebacterium glutamicum***.

Accordingly, in view of the reliability and comprehensive methods of functional characterization used by Applicants, and further in view of post-filing date experimental evidence confirming such characterization, Applicants submit that Applicants' identification of SEQ ID NO:5 and 6 as encoding a cysQ protein is accurate.

Lastly, Applicants submit that, similar to a ligase (the example provided in the Guidelines as having a well established utility), the function and use of a cysQ gene was well established in the art at the time of filing of the present application. Indeed, as taught in Neuwald *et al.* (1992) ("*cysQ*, a Gene Needed for Cysteine Synthesis in *Escherichia coli* K-12 Only during Aerobic Growth" *J. Bacteriol.* (1992) 174(2):415-425, a copy of which is attached herein as Appendix J), a cysQ gene is necessary for the synthesis of sulfite and cysteine by a cell, for example, by involvement in the uptake of sulfate, its subsequent activation, conversion to PAPS and eventual reduction to sulfite. Moreover, as taught by the specification and as was well known in the art at the time of the filing of the present invention, the intake, assimilation and processing of sulfur by a cell is critical for the production of fine chemicals, including amino acids, particularly those containing sulfur, such as cysteine and methionine (see, for example, page 54, line 29 to page 55, line 19 and Neuwald *et al.*). The importance of the cysQ gene is further magnified in view of cysteine's role as "the central precursor of all organic molecules containing reduced sulfur, ranging from the amino acid methionine to peptides, proteins, vitamins, cofactors such as S-adenosylmethionine, and hormones" (Snoeck *et al.* "Identification

of a Third Sulfate Activation System in *Sinorhizobium* sp. Strain BR816: the CysDN Sulfate Activation Complex" *Applied and Environmental Microbiology* 69(4):2006-2014 (2003), a copy of which is attached herein as Appendix K). Accordingly, based on the foregoing teachings in Applicants' specification and the general knowledge in the art at the time of the invention, one skilled in the art would immediately appreciate that the manipulation of the expression of the cysQ gene would serve to modulate the production of fine chemicals such as amino acids, vitamins and co-factors. Indeed, the activity and/or expression of cysQ molecules may be enhanced to increase the production of certain fine chemicals, for example, sulfur containing fine chemicals such as cysteine. Alternatively, the activity and/or expression of cysQ molecules may be reduced, or eliminated entirely to increase the production of other fine chemicals (see page 54, line 18 to page 55, line 19 of the specification).

In view of the foregoing and further in view of the standard for a well-established utility provided in Example 10 of the Guidelines, it is evident that the claimed invention possesses a well-established utility. Indeed, Applicants have characterized an open reading frame (*i.e.*, SEQ ID NO:5) based on homology analysis as encoding a protein (*i.e.*, a cysQ protein) with a well established function (*i.e.*, involvement in the uptake of sulfate, its subsequent activation, conversion to PAPS and eventual reduction to sulfite) and a well established use (*i.e.*, the production of fine chemicals). Accordingly, Applicants' invention has a well established utility that would have been readily apparent to one of skill in the art and, thus, Applicants respectfully request reconsideration and withdrawal of the foregoing rejection of claims 3, 9-17 and 36-38 under 35 U.S.C. § 101.

Rejection of Claims 3, 9-17 and 36-38 Under 35 U.S.C. § 112, First Paragraph (Enablement)

The Examiner has further rejected claims 3, 9-17 and 36-38 under 35 U.S.C. § 112, first paragraph as allegedly lacking enablement. In particular, the Examiner is of the opinion that

> [s]ince the claimed invention is not supported by either a specific and substantial utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. (Office Action, page 5).

Applicants respectfully traverse the foregoing rejection for the foregoing reasons. Initially, as indicated above, the claimed invention has a well established utility and, thus, one of skill in the art would, in fact, know how to use the claimed invention. Moreover, Applicants'

specification provides *ample* guidance as to how one of skill in the art would use the claimed invention.

For example, the specification provides extensive teachings that would allow a person of skill in the art to use and manipulate the cysQ gene to modulate the production of fine chemicals (see page 50, line 1 to page 57, line 7 of the specification). Specifically, Examples 4 and 5, at page 50, line 1 to page 51, line 34 of the specification, teach the mutagenesis of desired bacterial strains including, for example, *Corynebacterium* and *Brevibacterium* species, with modified cysQ molecules. Example 6, at page 52, lines 1-24 of the specification, describes techniques for identifying the expression of the modified cysQ molecules. Example 7, at page 52, line 26 to page 54, line 21 of the specification, describes techniques and culture and media conditions for growing bacterial strains. Example 8, at page 54, line 23 to page 55, line 13 of the specification, describes techniques for analyzing the effect of such modified cysQ molecules. Example 9, at page 55, line 15 to page 56, line 9 of the specification, describes techniques for analyzing the effect of modified cysQ molecules on the production of the desired fine chemical. Lastly, Example 10, at page 56, line 11 to page 57, line 11 of the specification, describes techniques for the purification and isolation of the desired product, *i.e.*, a fine chemical.

Moreover, at page 32, line 8 to page 38, line 2, the specification teaches various methods of designing vectors, for example, expression vectors, to transform various cells with the nucleic acid molecules of the present invention and further, methods for identifying and selecting those cells successfully transformed. Lastly, at page 46, line 12 to page 48, line 17, the specification teaches various methods for manipulating, for example, mutating, the nucleic acid molecules of the present invention to modulate the production of fine chemicals.

In view of the foregoing teachings in Applicants' specification, one skilled in the art would be able to make and use the claimed invention using only routine experimentation. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of the pending claims under 35 U.S.C. § 112, first paragraph, as lacking enablement.

Rejection of Claims 3 and 9-17 Under 35 U.S.C. § 112, First Paragraph (Written Description)

The Examiner has rejected claims 3 and 9-17 under 35 U.S.C. § 112, first paragraph as "failing to comply with the written description requirement." In particular, the Examiner is of the opinion that

> [w]ith the exception of SEQ ID NO:5, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides. Adequate written description requires more than a mere statement that it is part of the invention. The nucleic acid itself is required...
>
> Therefore, only SEQ ID NO: 5 but not the full breadth of the claim (or none of the sequences encompassed by the claim) meets the written description provision of 35 USC 112, first paragraph. (Office Action, page 6).

Applicants respectfully traverse this rejection on the grounds that, based on the teachings in Applicants' specification and the general knowledge in the art at the time of the invention, one skilled in the art would reasonably conclude that the Applicants were in possession of the claimed invention at the time the application was filed. In the interest of clarity, Applicants will address each aspect of this rejection below.

Rejection of Claims Directed to Nucleic Acid Molecules Comprising SEQ ID NO:5 or Encoding a Polypeptide Comprising SEQ ID NO:6

With regard to claims directed to nucleic acid molecules comprising the nucleotide sequence of SEQ ID NO:5 and to nucleic acid molecules encoding an amino acid sequence of SEQ ID NO:6, Applicants respectfully submit that claims 3(a) and 3(b) are sufficiently described in the specification in such a way to reasonably convey to one skilled in the relevant art that the inventors were in possession of the claimed genus of molecules at the time of the filing of the present application.

Applicants would like to direct the Examiner's attention to Example 8 of the *Revised Interim Written Description Guidelines Training Materials*. Example 8 sets forth a similar fact pattern as set forth in Example 10 of the *Revised Interim Utility Guidelines* (see above), *i.e.*, a sequence (SEQ ID NO:2) comprising a complete open reading frame that encodes SEQ ID NO:3 which has high homology to known DNA ligases. Based on the foregoing fact pattern, the *Revised Interim Written Description Guidelines* provide that

> [o]ne of skill in the art can readily envisage nucleic acid sequences which include SEQ ID NO: 2 because e.g. SEQ ID NO: 2 can be readily embedded in known vectors.

> Although there may be substantial variability among the species of DNAs encompassed within the scope of the claim because SEQ ID NO: 2 may be combined with sequences known in the art, e.g. expression vectors, the necessary common attribute is the ORF (SEQ ID NO: 2).
>
> Weighing all factors including (1) that the full length ORF (SEQ ID NO: 2) is disclosed and (2) that any substantial variability within the genus arises due to addition of elements that are not part of the inventor's particular contribution, taken in view of the level of knowledge and skill in the art, one skilled in the art would recognize from the disclosure that the applicant was in possession of the genus of DNAs that comprise SEQ ID NO: 2.

Accordingly, the Guidelines provide that where a claim is directed to a sequence comprising an open reading frame characterized, based on a homology analysis, as a protein of known function, the claim is sufficiently described in compliance with 35 U.S.C. § 112, first paragraph. Consistent with this standard, claims 3(a) and 3(b) are directed to complete open reading frames (*i.e.*, SEQ ID NO:5) encoding a full length cysQ protein (*i.e.*, SEQ ID NO:6). Accordingly, Applicants submit that claims 3(a) and 3(b) are sufficiently described in the present application so that one skilled in the art would appreciate that Applicants were in possession of the claimed invention at the time the application was filed. Applicants, therefore, respectfully request reconsideration and withdrawal of the rejection of claims 3(a) and 3(b), and claims depending therefrom, under 35 U.S.C. § 112, first paragraph as lacking written description.

Rejection of Claims Directed to Nucleic Acid Molecules Encoding Allelic Variants

The Examiner alleges that the genus of naturally occurring variants of claim 3 is not sufficiently described. In particular, the Examiner is of the opinion that

> [t]he claims are drawn to naturally occurring allelic variants of a polynucleotide encoding SEQ ID NO:6. The specification does not describe the sequence of any naturally occurring allelic variants of a polynucleotide encoding SEQ ID NO:6. The office is not aware of any prior art that shows a naturally occurring allelic variant of a polynucleotide encoding SEQ ID NO:6. The specification provides insufficient written description to support the genus encompassed by the claim. (Office Action, page 5)

In order to expedite examination, but in no way acquiescing to the validity of the Examiner's rejection, Applicants have cancelled claim 3(c) directed to nucleic acid molecules encoding naturally occurring allelic variants of a polypeptide comprising the amino acid sequence of SEQ ID NO:6, thereby rendering the rejection of this claim, and the claims

depending therefrom, moot. Notwithstanding the foregoing, Applicants wish to make the following remarks of record.

Applicants traverse this rejection on the grounds that, based on the teachings of the specification and the state of the art at the time of filing of the present application, one skilled in the art would reasonably conclude that Applicants were in possession of the genus of "naturally occurring variants" of polypeptides comprising SEQ ID NO:6 at the time the application was filed. Applicants respectfully disagree with the Examiner's characterization of the term "allelic variant" as described in the specification and known in the art. Applicants direct the Examiner's attention to page 26, line 34, to page 27, line 8 where Applicants define allelic variant as follows:

> In addition to the *C. glutamicum* MCT nucleotide sequences shown in Appendix A, it will be appreciated by one of ordinary skill in the art that DNA sequence polymorphisms that lead to changes in the amino acid sequences of MCT proteins may exist within a population (*e.g.*, the *C. glutamicum* population). Such genetic polymorphism in the MCT gene may exist among individuals within a population due to natural variation. As used herein, the terms "gene" and "recombinant gene" refer to nucleic acid molecules comprising an open reading frame encoding an MCT protein, preferably a *C. glutamicum* MCT protein. Such natural variations can typically result in 1-5% variance in the nucleotide sequence of the MCT gene. Any and all such nucleotide variations and resulting amino acid polymorphisms in MCT that are the result of natural variation and that do not alter the functional activity of MCT proteins are intended to be within the scope of the invention.

Applicants further note that patents, issued at the time of the filing of the present application, describe such naturally occurring variants in a consistent manner. Applicants direct the Examiner's attention to, for example, U.S. Patent No. 5,882,893, issued on March 16, 1999, in which independent claims 1, 14 and 15 are directed to "allelic variants." The specification of U.S. Patent No. 5,882,893 characterizes this term as follows:

> In addition to the mACHR-6 nucleotide sequence shown in SEQ ID NO:1 or 4, it will be appreciated by those skilled in the art that DNA sequence polymorphisms that lead to changes in the amino acid sequences of mACHR-6 may exist within a population (*e.g.*, the human population). Such genetic polymorphism in the mACHR-6 gene may exist among individuals within a population due to natural allelic variation... Such natural allelic variations can typically result in 1-5% variance in the nucleotide sequence of the mACHR-6 gene. Any and all such nucleotide variations and resulting amino acid polymorphisms in mACHR-6 that are the result of natural allelic variation are intended to be within the scope of the invention. Such allelic variation includes both active allelic variants as well as non-active or reduced activity allelic variants, the later two types typically giving rise to a pathological disorder. (Column 18, lines 3-32).

In view of the foregoing teachings in Applicants' specification and the art, Applicants submit that a skilled artisan would appreciate that the recitation of a specifically defined nucleotide sequence encoding a polypeptide is representative of the larger genus of nucleic acid molecules encoding naturally occurring allelic variants with similar structure and function. Accordingly, one skilled in the art would conclude that Applicants were in possession of the claimed naturally occurring allelic variants at the time of filing of the present application.

Rejection of Claims Directed to Sequences of 50% Identity to the Nucleotide Sequence of SEQ ID NO:5

With regard to claims directed to nucleotide sequences of at least 50% identity to SEQ ID NO:5, Applicants submit that claims 3(d) and 3(e) are sufficiently described in the specification in such a way to reasonably convey to one skilled in the relevant art that the inventors were in possession of the claimed genus of molecules at the time of the filing of the present application.

Applicants would like to direct the Examiner's attention to Example 14 of the *Revised Interim Written Description Guidelines Training Materials*. This example provides that a claim directed to variants of a protein having SEQ ID NO:3 "that are at least 95% identical to SEQ ID NO:3 and catalyze the reaction of A→B" with an accompanying specification that discloses a single species falling within the claimed genus, satisfies the requirements of 35 U.S.C. §112, first paragraph for written description. The rationale behind the foregoing conclusion, as presented by the *Written Description Guidelines*, is that "[t]he single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which Applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO:3 which are capable of the specified catalytic activity." The Guidelines also provide that "[t]he procedures for making variants of SEQ ID NO:3 are conventional in the art and an assay is described which will identify other proteins having the claimed catalytic activity. Moreover, procedures for making variants of SEQ ID NO:3 which have 95% identity to SEQ ID NO:3 and retain its activity are conventional in the art."

Similarly, in the present case, claims 3(c), 3(d), 39 and 40, and claims depending therefrom, are directed to nucleic acid molecules comprising a nucleotide sequence which is at least 90% or 95% identical to SEQ ID NO:5 and which code for polypeptides that have a cysQ

activity or nucleic acid molecules which code for polypeptides comprising an amino acid sequence which is at least 90% or 95% identical to SEQ ID NO:6 and which have a cysQ activity. The indication in Example 14 of the Written Description Guidelines that the production of polypeptides which contain a 5% variation from a specific sequence is routine in the art can be equated with the production of nucleic acid molecules which contain a 5% variation from a specific sequence. Furthermore, Applicants have disclosed in the instant specification assays for identifying all of the nucleic acid molecules of at least 90% or 95% identity to SEQ ID NO:5 which encode a polypeptide having a cysQ activity and all of the nucleic acid molecules encoding polypeptides of at least 90% or 95% identity to SEQ ID NO:6 and having a cysQ activity (see, for example, Examples 4-9 at page 50, line 1 to page 56, line 9 of the specification and Example 11 at page 57, line 9 to page 58, line 28 of the specification).

Accordingly, for at least the foregoing reasons, it would have been clear to one skilled in the art that Applicants were in possession of the claimed invention at the time the application was filed. Applicants, therefore, respectfully request reconsideration and withdrawal of the rejection of claims 3(c), 3(d), 39 or 40, and claims depending therefrom, as amended, under 35 U.S.C. § 112, first paragraph as lacking written description.

Rejection of Claims Directed to Nucleotide Sequences of 15 Contiguous Nucleotides

The Examiner further asserts that the genus of nucleotide sequences of at least 15 contiguous nucleotides of the nucleotide sequence of SEQ ID NO:5 is not adequately described such that one skilled in the art would reasonably conclude that the Applicants were in possession of the genus.

Applicants respectfully traverse the rejection on the following grounds. Applicants submit that based on the identification of the nucleotide sequence of SEQ ID NO:5 as set forth in the present application, one skilled in the art would be able to readily envision all fragments of at least 15 contiguous nucleotides in length that could serve as, for example, probes, primers, antisense molecules or enzymatically active fragments. Indeed, the specification teaches that nucleotide sequences of at least 15 contiguous nucleotides of SEQ ID NO:5 can be used as probes and primers (see page 24, lines 13-34 of the specification) in addition to use as antisense molecules (see page 29, line 26 to page 31, line 36 of the specification). Such fragments do not necessarily need to exhibit a cysQ activity. Instead, the ability of the claimed nucleotide

sequences to hybridize to strands of RNA or DNA, without necessarily exhibiting any enzymatic activity, renders the claimed nucleic acid molecules operative for purposes of the invention, for example, in inhibiting the activity of the cysQ molecules of the invention and thereby modulating the production of fine chemicals.

Moreover, Applicants submit that the present specification provides teachings sufficient to demonstrate that Applicants were in possession, at the time of filing, of the genus of fragments of at least 15 contiguous nucleotides of SEQ ID NO:5 which are, in fact, capable of encoding polypeptides exhibiting cysQ activity. At page 25, lines 21-37 of the specification, Applicants teach that such fragments could be designed by the incorporation of active domains of the cysQ protein that can participate in the metabolism of compounds necessary for the construction of cellular membranes in *C. glutamicum*, or in the transport of molecules across these membranes. Such domains were well known in the art at the time of the filing of the present application. For example, the domain [FWV]-x(0,1)-[LIVM]-D-P-[LIVM]-D-[SG]-[ST]-x(2)-[FYA]-x(0,1)-[HKRNSTY] (amino acid residues 78-92 of SEQ ID NO:6 encoded by nucleotide residues 332-376 of SEQ ID NO:5) had been identified at the time of filing of the present application as a highly conserved domain among cysQ ammonium transport proteins amongst various organisms including prokaryotes, eukaryotes and archaebacteria (see PROSITE entry for inositol monophosphatase, attached herein as Appendix L). Moreover, Example 8, at page 54, line 23 to page 55, line 13 of the specification, in addition to standard techniques known in the art at the time of the filing of the present application, provide means of identifying those fragments of at least 15 contiguous nucleotides which retain a cysQ activity.

For each of the foregoing reasons, Applicants submit that sequences of at least 15 contiguous nucleotides of SEQ ID NO:5, including fragments which encode polypeptides exhibiting enzymatic activity and, further, those that do not exhibit such activity, are sufficiently described to demonstrate to a skilled artisan that Applicants were in possession of the claimed sequences at the time of filing. Applicants, therefore, respectfully request reconsideration and withdrawal of the rejection of claim 3(e), and claims depending therefrom, under 35 U.S.C. §112, first paragraph, as lacking written description.

Rejection of Claim 37 Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claim 37 under 35 U.S.C. § 112, second paragraph as "being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention." In particular, the Examiner is of the opinion that

> [c]laim 37 is indefinite for recitation of the phrase 'wherein the nucleic acid molecule contains one or more nucleic acid modifications" because the extent of the modifications is not clear. It is not clear what the bounds of the genus of polynucleotides the claim encompasses. An extreme reading of the claim is that it includes polynucleotides with all possible sequences." (Office Action, page 7).

In the interest of expediting examination, but in no way acquiescing to the validity of the Examiner's rejections, Applicants have amended claim 37 to specify that the nucleic acid molecule of claim 37 encodes a polypeptide having a cysQ activity. Applicants submit that claim 37, as amended, is definite as to the scope of the genus of polynucleotides encompassed by the claim. Indeed, a skilled artisan would appreciate that the claim reads on those polynucleotides that differ by at least one nucleic acid modification from SEQ ID NO:5 yet still encode polypeptides having a cysQ activity.

Applicants submit claim 37, as amended, is sufficiently definite so as to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of the pending claims under 35 U.S.C. §112, second paragraph.

Provisional Rejection Under Judicially Created Doctrine of Obviousness-type Double Patenting

The Examiner has provisionally rejected claims 3 and 9-17 under the judicially created doctrine of obviousness-type double patenting "as being unpatentable over claims 1, and 8-17 of copending Application No. 11/055822." Specifically, the Examiner is of the opinion that

> [a]though the claims are not identical, they are not patentably distinct from each other because the copending claims are generic to the instant claims and copending application describes SEQ ID NO: 989 that meets the limitations of both the copending and instant claims referred to above... (Office Action, page 9).

While in no way acquiescing to the Examiner's rejections under the judicially created doctrine of obviousness-type double patenting, Applicants note that prosecution of the present

application and co-pending Application No. 11/055822 may render this rejection moot. Accordingly, once the pending claims in the present application are formally indicated as otherwise allowable, and should such submission(s) be necessary, Applicants will consider submitting a terminal disclaimer in compliance with C.F.R. §§ 1.321(b) and (c), if appropriate, which will obviate this rejection.

CONCLUSION

In view of the foregoing remarks, reconsideration of the rejections and allowance of all pending claims is respectfully requested. If there are any remaining issues or if the Examiner believes that a telephone conversation with Applicants' Attorney would be helpful in expediting prosecution of this application, the Examiner is invited to call the undersigned at (617) 227-7400.

The Commissioner is hereby authorized to charge any deficiency in the fees paid herewith, or credit any overpayment, to Deposit Account No. 12-0080, under Order No. BGI-125CPCN, from which the undersigned is authorized to withdraw.

Dated: **August 14, 2006**

Respectfully submitted,

By _____

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